**REMARKS**

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Claim Amendments

Claims 1, 34, 37, 38 and 40 are amended.
Claims 33, 39 and 41 through 43 are cancelled.
Claims 2 through 5, 7 and 8, and 11 through 20 were previously cancelled.
Claims 6, 9 and 10 were previously withdrawn as drawn to an non-elected invention.

In view of these amendments, Claims 1 and 21 through 32, 34 through 38, 40 and 44 through 46 are now pending in the application. The claims cancelled in this amendment are being removed from consideration only to expedite allowance of the remaining claims as amended; therefore, cancellation of the claims is not intended to be, and should not be regarded as, acquiescence in the basis of the previous rejections applied thereto.

No new matter is introduced by these amendments. Entry thereof is therefore requested.

II. Response to Rejection of Claims 1 and 33-46 under 35 USC 112, first paragraph (enablement).

A. Governing Law.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

- the breadth of the claims,
- the nature of the invention,
- the state of the prior art,
- the level of one of ordinary skill,
- the level of predictability in the art,
- the amount of direction provided by the inventor,
- the existence of working examples, and
- the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

In *Wands*, the court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." 8 USPQ2d at 1407.

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. 8 USPQ2d at 1404, 1407.

Here, there is no question that the level of skill in the art of gene therapy is very high, and that Applicant has provided evidence demonstrating successful practice of the techniques utilized in practicing the invention. Indeed, the basic technique utilized has already been patented by Applicant (see, e.g., US Patent No. 6,815,431). Therefore, the only issue as to enablement, as raised in the Office Action, is whether the breadth of the claims is commensurate with the scope of the teaching provided. As discussed below, Applicant submits that the answer to that question is clearly 'yes'.

B. The Claims are Commensurate in Breadth with the Scope of the Enabling Teaching Provided.

The Office Action states that the specification is "enabling for improving motor function and neuronal density of Parkinson Disease (PD) monkey model or Alzheimer's disease (AD) monkey model by injecting lentiviral vector encoding GDNF and NGF, respectively, into preselected brain regions of said monkey." Action at page 2, second numbered paragraph. Referring to the Declaration of Dr. Mark Tuszynski submitted with the previous Amendment and to related U.S. Patent No. 6,815,431, the Action indicates that those documents demonstrate anterograde transport of an expression product from the striatum to the substantia nigra but not a corresponding "amelioration of neuronal atrophy or stimulation of neuronal growth activity in innervated neurons *that are distant from neurons expressing a neurotrophin protein* via non-chemotropic action [thereof]." Action at page 5, first paragraph, emphasis added.

Applicant respectfully notes that the italicized portion of the foregoing passage from the Office Action appears to reflect an understanding of the invention that differs from how it is defined by the claims. In particular, the Action refers to the invention as being directed to administering a neurotrophin to one neuron to influence growth in other neurons. However, the claims are directed to the inventor's discovery that a neuron which takes up a neurotrophin-encoding recombinant expression vector at one site (e.g., at the neuronal body) can experience growth at a another site (the axonal termini) within the same neuron. The neuron may be one that innervates another region of the brain, so uptake occurs in one region and growth in another (see, Claim 1). The invention thereby enables a clinician to administer a neurotrophin to a relatively accessible region of the brain to influence activity in a more remote region of the brain that is innervated by the treated neuron.

In this respect, the claims are fully supported by the Specification. For example, Example II provides data demonstrating that "[t]hese effects of cellularly-delivered NGF on cortical cholinergic innervation were exerted at a distance, since the growth factor was presented to the cholinergic soma yet influenced terminal axon density in the distant cortex. Remarkably, reversal of age-related axonal attenuation in both the soma and the cortex was achieved after only three months of NGF delivery to the primate brain soma. Thus, practice of the invention significantly and efficiently ameliorates neuronal loss accompanying the normal aging process in the primate brain." (Specification at page 6, lines 24-30, emphasis added).

Thus, the Specification itself provides ample evidence of enablement for use of NGF in the by its delivery to the cholinergic soma to ameliorate neuronal loss in the distant cortex. In previous Office Actions, however, the Examiner queried whether the invention was enabled for use of neurotrophins other than NGF, for delivery of such neurotrophins by means other than grafting of donor cells (the particular technique utilized in Example II), for treatment of neurons other than cholinergic and dopaminergic neurons, and/or for use to treat conditions other than normal aging. In response to those queries, Applicant submitted additional evidence, i.e., the Declaration of

Mark Tuszynski, several literature reference and evidence of human clinical trial outcomes from use of the invention, and also made reference to one of the inventor's issued patents to an *in vivo* practice of the invention generally (US Patent 6,815,431).

With respect to the Tuszynski Declaration, the purpose of its submission was not, as the Action appears to suggest, to demonstrate that a neurotrophin delivered according to the invention would stimulate axonal termini growth. That is the claimed subject matter that is already demonstrated by the Specification. Rather, the Tuszynski Declaration was submitted to, and does, demonstrate that delivery of neurotrophins according to the invention (i.e., by in vivo delivery using a recombinant expression vector) is effective to achieve (a) uptake and expression of the encoded neurotrophin; and (b) therapeutic benefits such as neuronal growth (density increase) and functional improvements (motor function) in art-accepted models of neurodegenerative disease in humans (AD and PD). In other words, the Tuszynski Declaration therefore supports Applicant's assertion that the invention as claimed is enabled as to its starting point (neuronal uptake and neurotrophin expression) and a therapeutic end point.

As to the '431 Patent, its teachings support Applicant's position that the non-chemotropic neuronal growth achieved in the invention can occur not only in cholinergic neurons (e.g., transversing the forebrain and cortex) but also in dopaminergic neurons (e.g., transversing the striatum and substantia nigra).

As to the evidence previously submitted with respect to the inventor's success in using the invention claimed in this and related patents in treating conditions such as AD, the Action states that "the human clinical trial data fails to demonstrate that the slowing down of AD progression in human patient is due to the non-chemotropic action of the expressed exogenous neurotrophin, or such data is just the effect of the expressed neurotrophin in the target neurons at the delivery sites." Action at page 7, first paragraph.

Applicant respectfully submits that the purpose of supplying evidence concerning the human clinical outcomes was not as described in the Action; i.e., to establish a direct link between the non-chemotropic effects observed through the invention and the improvement in the AD patients treated. Rather, the clinical trial evidence was submitted to demonstrate that practice of the starting point of the invention—administration of an neurotrophin to the brain—can produce clinically significant improvements in a patient population whose needs are critical, but unmet by current therapeutic modalities. As such, the overall approach taken by the invention as taught—gene therapy to stimulate neuronal growth and activity—can and has been successfully practiced as described.

However, the Office Action rejects the clinical trial evidence submitted on the basis that it does not demonstrate a direct link between the axonal growth achieved in the invention and the clinical outcomes. Yet Applicant need not prove how the invention works, nor that it is efficacious (see, e.g., *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("[t]esting for full safety and effectiveness of [an invention] is more properly left to the [FDA]."). Rather, the Applicant need only satisfy the statutory requirements of the patent law, such as enablement for practice for the claimed technique and a utility, such as the stimulation of axonal growth whose achievement has been amply demonstrated.

Lastly, as to the literature references relied upon by Applicant in the previous Amendment, the Examiner's concern seems to lie with whether they, together with the Specification, demonstrate that the invention can be used to treat a wide variety of neurons in the brain, such as those listed in the Action at page 3, second paragraph. Without conceding the basis of the rejection in this respect, the claims have been amended to facilitate early allowance to specify that the targeted neurons are cholinergic or dopaminergic ones whose susceptibility to treatment with the invention has been demonstrated by the evidence of record.

For all of the foregoing reasons, Applicant submits that Claims 1 and 34-38, 40 and 44-46 (the claims of the set at issue remaining after amendment) are fully enabled. Reconsideration and withdrawal of the rejection of the claims under Section 112, first paragraph is therefore respectfully requested.

III. Response to Rejection of Claims 1 and 21-32 under 35 U.S.C. Section 112, first paragraph (enablement).

Claims 1 and 21-32 are rejected for lack of enablement on essentially the same grounds put forth with respect to Claims 1 and 33-46.

Claims 21-32 now depend from Claim 1. Claim 1, and the subject matter of its dependent claims, are fully addressed by the arguments and amendments made in the preceding paragraphs. Therefore, for the same reasons discussed above, Claims 1 and 21-32 are fully enabled.

Reconsideration and withdrawal of the rejection of such claims under Section 112, first paragraph, is therefore respectfully requested.

**CONCLUSION**

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check

being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date June 13, 2006

By

Stacy L. Taylor
Attorney for Applicant
Registration No. 34,842

FOLEY & LARDNER LLP
P.O. Box 80278
San Diego, California 92138-0278
Customer No. 30542
Telephone: (858) 847-6720
Facsimile: (858) 792-6773

Enclosures: Clean copy of amended claims